REMARKS

Applicants have amended the specification to replace the sequence listing of record with the substitute sequence listing submitted herewith. Applicants have amended the specification to insert sequence identifiers corresponding to the substitute sequence listing where appropriate. Thus, the amendments to the specification do not constitute new matter.

Claims 1, 15, 20-24, 26-28, 30-38, 45 and 60-70 were pending in the instant application. Applicants have amended claims 1, 15, 24, 61 and 62-70, and have added new claim 71, for uniformity, clarity and to more particularly point out and distinctly claim that which the Applicants regard as the invention. Applicants have canceled claims 20, 45 and 60 in view of the amendments submitted herewith without prejudice and reserve the right to pursue the subject matter of the canceled claims in one or more related applications. Support for the amendments to the claims is found throughout the specification as filed. For example, support for the amendments to claims 1, 15 and 60 may be found, *inter alia*, in paragraphs [0007]-[0009] at page 2, and in paragraph [0059] at page 15; support for new claim 71 may be found, *inter alia*, in paragraph [0054] at page 14, in paragraphs [0056]-[0057] at pages 14 to 15, and in paragraph [0059] at page 15. Accordingly, no new matter has been introduced. After entry of this amendment, claims 1, 15, 21-24, 26-28, 30-38, and 61-71 will be pending.

The rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn

The Examiner has rejected claims 15, 20-24, 26-28, 30-31, 45 and 60 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Preliminarily, Applicants note that claims 20, 45 and 60 have been canceled, rendering the instant rejection moot with respect to these claims. The Examiner contends that while the specification is enabling for the specific secretase inhibitors L-685,458, DAPT and DAPM, JLK-6, OM99-2, Z-VLL-CHO, GL189 and P10-P4'statV, the specification does not reasonably provide enablement for other secretase inhibitors. In particular, the Examiner alleges that because the mechanism of action by which the secretase inhibitors inhibit angiogenesis is unknown, it would be unduly burdensome to determine the anti-angiogenic effects of any secretase inhibitor. Applicants respectfully disagree with the Examiner's position.

Applicants point out that under the applicable case law, it is improper to limit Applicants to the specific example presented, notwithstanding the disclosure and enablement of a broader invention. See In re Anderson, 176 U.S.P.Q. 331, 333 (C.C.P.A. 1973); In re Kamal, 158 U.S.P.Q. 320, 323 (C.C.P.A. 1968). The test for enablement is whether one reasonably skilled in

the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. U.S. v. Telectronics Inc., 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."). One skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." Phillips Petroleum Co. v. United States Steel Corp., 673 F. Supp. 1278, 1291 (D. Del. 1991); see also DeGeorge v. Bernier, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. Fields v. Conover, 170 USPQ 276, 279 (CCPA 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Applicants point out that enabling support for the claimed methods is provided throughout the specification in form of guidance on how to identify a secretase inhibitor that exhibits anti-angiogenic activity and how to use said inhibitor to effect a reduction in tumor volume. In particular, Applicants direct the Examiner's attention to the working examples of methods to identify anti-angiogenic secretase inhibitors in Examples 1-3, at pages 16-22 of the specification. Moreover, Applicants point out that neither secretase inhibitors nor methods of screening for compound exhibiting such inhibitory activity (in particular, with respect to γ- and β-sectretase) were novel subject matter at the time of filing the instant application. In fact, secretase inhibitors were well known in the art as potential therapeutics for a variety of conditions, in particular, Alzheimer's disease. Applicants respectfully direct the Examiner's

attention to Dash et al., 2003, Crit. Rev. Biochem. Mol. Biol. 38:89-119 ("Dash") and Tsai et al., 2002, Curr. Med. Chem. 9:1087-1106 ("Tsai") (references **C17** and **C19**, respectively in the supplemental Information Disclosure Statement ("IDS") submitted concurrently herewith). Dash and Tsai are review articles presenting the state of the art of aspartic peptidase inhibitors (*e.g.*, β-secretase inhibitors) and γ-secretase inhibitors, respectively. As demonstrated by Dash and Tsai, the art recognized numerous secretase inhibitors (including multiple γ- and β-secretase inhibitors) beyond those listed in the specification. Given the detailed teachings in the specification as described above, the state of the art with respect to secretase inhibitors, and the high level of skill in the art, Applicants submit that the experimentation to make and use the claimed methods throughout their scope would be merely routine and thus, the full scope of the claimed methods is enabled.

In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been obviated or overcome both with respect to claims 15 and 61, and with respect to claims 21-24, 26-28, 30-31, and 62-71 as dependent thereon, and should be withdrawn.

The rejections under 35 U.S.C. § 103(a) should be withdrawn

The Examiner has rejected claims 15, 20-27, 30-31, 45 and 60-70 under 35 U.S.C. § 103(a) as allegedly obvious over either Jundt et al., 2002, Blood 100:158 ("Jundt") or Weng et al., 2003, Mol. Cell Biol. 23:655-664 (Weng"). The rejection is predicated on the assertion that either Jundt or Weng provides motivation to use a secretase inhibitor to treat a solid tumor in an animal or human. Applicants respectfully disagree with the Examiner's contentions.

Jundt is directed to a characterization of Jagged1-Notch signaling in Notch-positive Hodgkin and large cell anaplastic lymphoma cell lines. In the sole inhibition study presented, Jundt reports that, *in vitro*, exposure of these highly proliferating cell lines to Jagged1 (which, according to Jundt, elicits Notch signaling) results in an exponential increase in the cells' respective growth rates, which effect is blocked by the γ-secretase inhibitor, DAPT. Importantly, however, Jundt reports that only the increase in growth rate is blocked by DAPT, indicating that the original proliferative capacity of the cells is unchanged by exposure to DAPT. Accordingly, Jundt cannot teach or suggest a method to control tumor cell growth using DAPT, much less a method to reduce solid tumor volume comprising the use of at least one secretase inhibitor as instantly claimed in claims 1, 15 and 61, and claims 21-23, 26-28, 30-31 and 62-71 as dependent

thereon.

Similarly, Weng fails to render obvious the instantly claimed invention. Weng discloses the use of recombinant T cell lines transformed to express Notch-constructs in a study of Notch signaling in regulation of cell growth and differentiation. In particular, Weng reports that presenilin inhibitors alter processing of the Notch constructs and that one specific such inhibitor, DPF-AA, was able to suppress the growth of one of the recombinantly created cell lines. The Examiner points to the abstract; page 662, column 2, lines 13-16; page 663, column 1, lines 1-59 and column 2, lines 1-17 as evidence that Weng teaches a method of "treating a tumor ... comprising administering to the animal or human a therapeutically effective amount of a secretase inhibitor effective ... to reduce tumor volume" (see Office Action page 6, 3rd full paragraph); however, Applicants respectfully point out that these passages teach the use of presenilin inhibitors as growth inhibitors only in the recombinant, *i.e.*, Notch-transformed cell lines and, thus, suggest nothing with respect to the inhibition of growth in non-recombinant cancers. In fact, with respect to other cancers, Weng specifically discloses that such inhibitors are of use as *screening tools* for the further elucidation of Notch signaling (see, page 662, column 2, line 13 to page 663, column 1, line 6 and page 663, column 3, lines 14-17). Thus, like Jundt, Weng does teach or suggest a method to reduce solid tumor volume comprising the use of at least one secretase inhibitor as instantly claims in claims 1, 15 and 61.

Moreover, assuming, *arguendo*, that Jundt or Weng would suggest the use of a secretase inhibitor in the treatment of a cancer, neither reference suggests the use of a secretase inhibitor to reduce the volume of a solid tumor as instantly claimed in claims 1, 15 and 61. As discussed *supra*, Jundt and Weng disclose studies conducted using lymphoma and recombinant lymphoblastic cell lines, respectively. As understood by one of skill in the art, lymphomas and/or lymphoblastic neoplasms are hematopoietic cancers, which cancers manifest as dispersed, non-solid malignancies. In contrast to solid tumors, as a dispersion of malignant cells, hematologic malignancies are not defined by a the solid tumor microenvironment. It is understood that this microenvironment contributes in large part to the chemotherapeutic resistance observed in sold tumors (see, *e.g.*, Tsuro et al., 2003, Cancer Sci. 94:15-21 ("Tsuro"), Section 2 at page 16; reference **C20** in the supplemental IDS submitted concurrently herewith). Tsuro presents an outline of concerns facing the chemotherapeutic treatment of solid tumors, in particular, contrasted against the success noted for chemotherapy in hematologic malignancies (see, *e.g.*, Tsuro abstract and introduction at page 15). Accordingly, when viewed by one of skill

in the art, the alleged reporting of Jundt or Weng of controlling proliferation of hematopoietic cell lines is not suggestive of a method of treating solid tumors.

The Examiner further contends that, despite being completely silent with respect to angiogenesis in any context, Jundt and Weng separately render obvious a method of treatment of a tumor by inhibiting angiogenesis. In response, Applicants respectfully submit that, despite the Examiner's contentions and in view of the state of knowledge of the art at the time of filing the instant application, the references, in fact, teach away from the invention as instantly claimed. As amended herein, the instantly pending claims are directed to a method of reducing solid tumor volume in an animal or human. As was known in the art, and as is taught in the instant disclosure, the solid tumor growth is dependent on angiogenesis. At best, Jundt or Weng teach the modulation of growth rate in a specific cancer cell line *in vitro* by inhibition of Notch signaling. However, Notch signaling was known at the time of filing of the instant application to negatively regulate microvessel angiogenesis. Applicants respectfully direct the Examiner's attention Leong et al., 2002, Mol. Cell Biol. 22:2830-2841 ("Leong") and WO 97/45143 to Zimrin et al. ("Zimrin"), submitted as references **C18** and **B01**, respectively, in the supplemental IDS submitted concurrently herewith (Leong and Zimrin were also previously submitted as Exhibit B and C, respectively, in the Amendment dated September 30, 2005 in connection with the prosecution of the instant application). Leong demonstrates that activation of Notch in human microvascular endothelial cells inhibits endothelial sprouting and VEGF-induced angiogenesis (see, *e.g.*, Leong, abstract), while Zimrin teaches that Notch signaling inhibits the migratory phase of angiogenesis in bovine microvasculature endothelial cells. Accordingly, one of skill in the art would expect the inhibition of γ-secretase (and consequential inhibition of Notch signaling) as taught by Jundt or Weng to result in, at best, no activity or, at worst, enhanced angiogenic activity. Thus, in the context of a subject with a solid tumor, administration of γ-secretase inhibitors would be expected to have therapeutic effects ranging from no activity to a counter-indication, *i.e.*, enhancement of tumor volume due to stimulation of angiogenic activity. In view of the foregoing, Applicants submit that, prior to the disclosure of the instant application, one of skill in the art would have had no reasonable expectation that secretase inhibitors would effect a inhibition of angiogenesis, much less that secretase inhibitors could be used to therapeutically reduce tumor volume as instantly claimed in claims 1, 15, and 61.

In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. § 103(a)

have been obviated or overcome with respect to claims 1, 15 and 61, and with respect to claims 21-23, 26-28, 30-31 and 62-71 as dependent thereon, and respectfully request withdrawal of the instant rejections.

CONCLUSION

Applicants respectfully request that the amendment and remarks made herein be entered and made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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